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Review Article

Effects of Obesity on Cancer Progression by Affecting the Immune System

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Abstract

The prevalence of obesity has been increasing in the last few decades, and it is regarded as one of the major health problems in the world. The rising prevalence of obesity in children and adults is a result of eating disorders and the changes related to the modern lifestyle. Obesity alters the adipocytes' substance secretion, which affects the function of the immune system and leads to obesity-induced inflammation and the development of obesity-related cancers. Altered chemokines, adipokines, and conditions like insulin resistance are most likely related to the impaired immune system in the obesity state. The impaired secretion of adipokines, such as increased leptin and reduction in adiponectin, affects innate immune system antitumor responses after long-term exposure. In addition, changes in chemokines and, consequently, the promotion of insulin resistance create an immunosuppressive environment that debilitates the host to fight against tumor growth, progression, and metastasis. Accordingly, it may increase cancer susceptibility in obese individuals. Thereby, it can be concluded that treatment of obesity will greatly affect the improvement of immune system function and, as a result, may possibly reduce the risk of cancer. The aim of this study is to review the pathways resulting in impaired immune system and inflammation and their link to cancer progression in obesity. Several hypotheses have been proposed to have a critical contribution to the development of obesity-related cancers, such as the function of cytokines, insulin resistance, and NF-κB and senescence changes in obesity. These hypotheses will be discussed later in this article.

Keywords: Obesity; Cancer Progression; Inflammation; Adipokines; Cytokines; Insulin

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Introduction

The immune system protects the body from foreign substances and pathogenic microorganisms like bacteria, viruses, etc. Moreover, it plays a key role in the prevention of cancer development and progression. Therefore, the immune system is equipped to recognize both foreign invaders and abnormal cells. The immune system is divided into two major subgroups: innate immunity and adaptive immunity. The innate immune system is well known for urgent and non-specific responses, while adaptive immunity takes more time to develop a specific response. The innate immune system in humans contains different leukocytes like monocytes, basophils, eosinophils, neutrophils, and natural killer cells (NK). These components mainly initiate inflammation (1). NK cells and macrophages have a main role in controlling damaged cells and cancer cells (2). Natural killer T cells (NKT) that have structural and functional similarities to both NK (innate immunity) and T cells (adaptive immunity) have been detected to play an important role in tumor immunity (3). Altered diets in modern lifestyles can have an effect on the epigenetic state of genes, which might increase or decrease cancer risk factors (5). One of the most common types of altered diets in modern lifestyles is over-nutrition. Over-nutrition is a type of malnutrition, and the amount of nutrients, especially macronutrients, exceeds the daily requirements. The adverse impact of over-nutrition on the immune response has been frequently proven. Some literature suggests that a series of immune mechanisms that operate against cancer are impaired by obesity-dependent alternations, which can increase the risk of the development and progression of cancer (6,7). Due to the strong link observed between nutrition, immune function, and cancer, in this review, we will investigate the pathways resulting in impaired immune function and the main reasons behind impaired immune response and cancer progression in obesity.

Nutrition and Immune System

Recent studies suggest that environment and diet can have a direct impact on the immune system (7,8). The importance of diet and nutrition in the prevention of cancer is widely recognized (8), and it has been observed that it is strongly correlated with increased immune dysfunctions and risk of several types of cancer. Nutritional components of diet can affect cancer development by fundamental cellular processes alteration that have an influence on hormonal factors modulating gene expression, such as tumor-suppressor genes, regulators of cell proliferation, apoptosis, etc. (8). Immune system requires appropriate food intake in order to function properly. Accordingly, high fat diet (HFD) and increased free fatty acids in circulation lead to weight gain and obesity, which in turn cause immune system-induced inflammation (9). Obesity is the common underlying cause of chronic inflammation (10). In an obesity state, Immune cell cytokines such as macrophages, cytotoxic T cells, and NK cells promote tumor growth and progression, enhance cell proliferation and metastasis, and also impair the NK cell's function, which leads to health complications (11).

Obesity is specified by increased insulin production and growth factors, low-grade chronic inflammation, and pro-inflammatory cytokine secretion that regulates the development and progression of cancer (12). Excess nutrient delivery to adipose tissue triggers adipocyte expansion **(Figure 1)** and outcomes in adipose-derived hormones being altered and chronic inflammation developed (13). Animal models recapitulating Human cancers, such as transgenic murine models with intact immune functions, gave important indications of the critical roles of TNF-α and IL-6 cytokines, highlighting the key roles played by the master transcription factors NF-kB and STAT3 in the relationship among chronic inflammation and cancer. Macrophage infiltration of these cytokines into the tumor microenvironment is now recognized as an important driver of cancer progression, and tumor-associated macrophages (TAM) conform to increased angiogenesis, metastasis, and decreased breast cancer patient survival (12).

Obesity as a common clinical problem is related to increasing risk of type2 diabetes mellitus, hypertension, cardiovascular and special types of cancers such as esophageal adenocarcinoma, cancer of the colon, and postmenopausal breast cancer (14-17). Obesity is a chronic subclinical condition of inflammation. In this condition, the growing white adipose tissue (WAT) plays a ma-

jor part in the progression of obesity-related inflammation through dysregulated secretion (both adipocyte and non-adipocyte) of pro-inflammatory and anti-inflammatory cytokines, chemokines, and adipokines (18, 19). Inflammation also contributes to the increasing risk of mortality for obesity-associated cancers. Thus, chronic inflammation sets the stage for cancer (20). Mechanisms that cause cancer and obesity to be associated are not fully acknowledged. There were several hypotheses suggested to have a critical contribution to the development of obesity-related cancers, such as the function of cytokines, insulin resistance, and NF-κB and senescence changes in obesity. These hypotheses will be discussed later in this article.

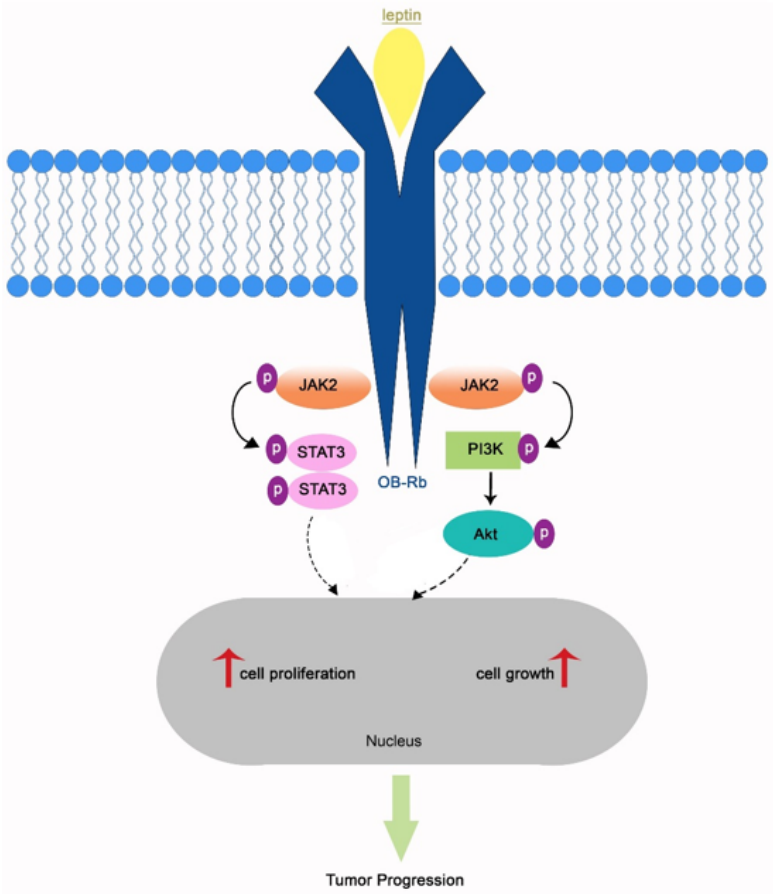

Figure 1. Leptin, JAK/STAT, and PI3K/Akt pathways and tumor progression

Obesity and cancer

Adipose tissue is one of the important endocrine organs, which is capable of secreting adipokines. The two main types of adipokines are adiponectin and leptin. Regulation of tumorigenesis, inflammation, and tumor microenvironment by adipocytes can take place via chemokines and cytokines. Expansion of adipose tissue during obesity causes adipose dysfunction and increased levels of pro-inflammatory factors. Obesity is a state followed by inflammation, which increases lipolysis and insulin resistance. Also, altered adipokines and chemokines such as IL-6, TNF-α, etc. (29) promote tumor growth (20, 34).

Adipokines

Previous studies have shown that adipokine activity appears to have a key role in immune system function and the development of tumor proliferation (35). Upon the expanding white adipose tissue, some changes occur in leptin and adiponectin secretion, which have significant effects on the immune system. Adiponectin is a peptide hormone derived from white adipose tissue (WAT) and less from endothelial cells. It has anti-inflammatory and insulin-sensitizer effects. Unlike other adipokines, its level in blood is inversely associated with body mass index (BMI), fat mass, and insulin resistance. Concerning this

fact, circulating adiponectin declines in obesity (36, 37). Despite its unknown characteristics in the etiology of cancer, current evidence shows that reducing levels of adiponectin increases the risk of obesity-related cancers (38, 39). Adiponectin inhibits endothelial NF-kB signaling and TNF-α production. In addition, it stimulates the release of anti-inflammatory cytokines like IL-10 and IL-1 (14, 40, 41). It seems that adiponectin administration suppresses cell proliferation and induces anti-tumor activity by increasing apoptosis in cancer cells (42). By contrast, leptin is a satiety hormone which controls energy expenditure. It has been reported that Leptin serves as a significant energy homeostasis regulator by reducing satiety and increasing energy costs (43). In addition to its metabolic functions, it has been shown that leptin acts to modulate the immune system functions, e.g., NK lymphocyte functions and production of pro-inflammatory cytokines such as TNF-α, IL-6, IL-12 (44, 45). It has been shown that leptin regulates body weight and the immune system via targeting the leptin receptor (OB-R) (46). The Leptin binding OB-R leads to the activating kinase-signal transducer and transcription factors (JAK/STAT) **(Figure 2)**, which can promote cell proliferation, migration, and incursion differently in vitro and in vivo in cancer models. Hyperlipidemia and leptin resistance are highly associated with excess weight gain (47). The effect of leptin on human NK cell function, especially in obesity, remains unknown. However, studies revealed reduced secretion of IFNγ via NK cells during leptin resistance or chronic elevation of leptin (48). In general, leptin is a well-known factor that can stimulate cell proliferation and suppress programmed cell death by apoptosis. Therefore, it plays the same role for NK cells as well (48-50).

Immediately after binding leptin to OBR, the activated receptor of JAK mediates JAK phosphorylation while also phosphorylating the intracellular tail of the receptor. This leads to the recruitment of specific STATs (STAT3), which are then also activated through phosphorylation. Activated STATs are released from the receptor, translocate to the nucleus, and bind to the DNA-promoter regions of target genes. Meantime, phosphatidylinositol 3-kinase (PI3K) products typically stimulate protein kinases such as Akt to phosphorylated form. JAK/STAT and PI3K/AKt are critical in cancer stem cell (CSC) biology by inducing proliferation, cell growth, and inhibition of apoptosis in tumor cells.

Macrophages and Natural Killer (NK) cells

In obesity, proinflammatory macrophages accumulate in adipose tissue and cause chronic low-grade inflammation there (21). Macrophages are an important component of the microenvironment of the tumor and orchestrate different aspects of immunity. In reaction to environmental indications, macrophages can reversibly change their endotypes containing hypoxia and stimuli obtained from other immune cells, similar to the extracellular matrix. Depending on their activation status, macrophages can have dual effects on tumorogenesis, either by antagonizing the cytotoxic activity of the immune cells or by increasing the response of anti-tumors. Based on their activation status, macrophages may have double effects on tumorigenesis, either by antagonizing the cytotoxic activity of immune cells or by enhancing the immunomodulatory response (22). Also, enlarged white adipose tissue has been shown to play a major role in the progression of chronic inflammation by increased secretion of pro-inflammatory cytokines, e.g., interleukin 6 (IL-6), IL-1, tumor necrosis factor alpha (TNF-α), chemokines such as monocyte chemotactic protein 1 (MCP-1) and also adipokines: leptin, vistatin, resistin and vascular endothelial growth factor (VEGF). By contrast, it has a major effect on the decrement of ant-inflammatory adipokines like adiponectin and IL-10 (23-25). Furthermore, obesity alters the immune cell population in a way that despite increasing the total number of T and B lymphocytes, the number of helper T cells, type 2 lymphocytes, regulatory T lymphocytes, and eosinophils are significantly reduced, which shows a trend toward the development of an inflammatory microenvironment (26, 27). NK cells, as a part of innate immunity, are able to destroy tumor cells, modulate tumor growth, and inhibit metastasis. As a result of disturbed adipocytes, the blood level of NK cells is significantly reduced. It has been reported that NK cells produce interferon γ (IFNγ) in response to inflammation and with exposure to infected cells and obesity-related changes. They also alter macrophage pheno-

types from M2 or alternatively activated macrophage with anti-inflammatory role - to M1 - or generically activated macrophage, which plays a pro-inflammatory role. It seems that NKT cells produce IFNγ, which is anti-metastasis. However, in obese individuals, decreased counts of NKT cells and also their impaired protection activity have been observed (29, 30). NKT cells are classified into two groups: NKT type I cells that act as both protective and pathogenic factors in diseases (like), and NKT type II cells that have been shown to promote intestinal inflammation (31). In many human cancers, small concentrations of circulating type I NKT cells correlate with bad perspective, which is why these cells were targeted in a sequence of clinical studies (32). In some types of cancer, NKT cells of type I and II play opposing roles, while NKT cells of type I encourage NKT cells of type II to suppress tumor immunity. IL-13 production mediated immunosuppression by type II NKT cells resulted in the activation of TGF-β-secreting Gr1+CD11b+ myeloid-derived suppressor cells (MDSCs), which in turn suppressed tumor-specific CD8 + T cells or type I NKT cells (33). Recent studies have found that the distribution of both subsets of NKT is related to cancer progression. Studies have reported that cancer patients with BMI>40 have more type I NKT cells in comparison to the lean control group.

Pro-inflammatory Cytokines

As discussed above, two main pro-inflammatory cytokines involved in adiposity inflammation state are TNF-α and IL-6. TNF-α as a pro-inflammatory cytokine is primarily produced by monocytes, macrophages and also other cells such as T, B and NK lymphocytes. In adipose tissue, it is mainly produced by adipose tissue macrophages (30, 51, 52). Overproduction of TNF-α in inflammation blocks insulin signaling and increases insulin resistance. It has been proven that under specific conditions like being overweight, TNF-α can act as a tumor promoter and boost tumorigenesis (53).

IL-6 levels have been observed to increase with obesity and aging. It has effects on NK cell production and suppression of Tregs levels (54-56). The secretion of IL-16 leads to the development of migration, invasion of cancer cells, and tumor growth (57). It regulates the activity of the JAK-STAT pathway and, as a result, promotes cancer cell proliferation and angiogenesis (58). These mechanisms promote toxic microenvironments in adipose tissue that are in favor of tumor growth (59, 60). In addition, levels of circulating pro-in-

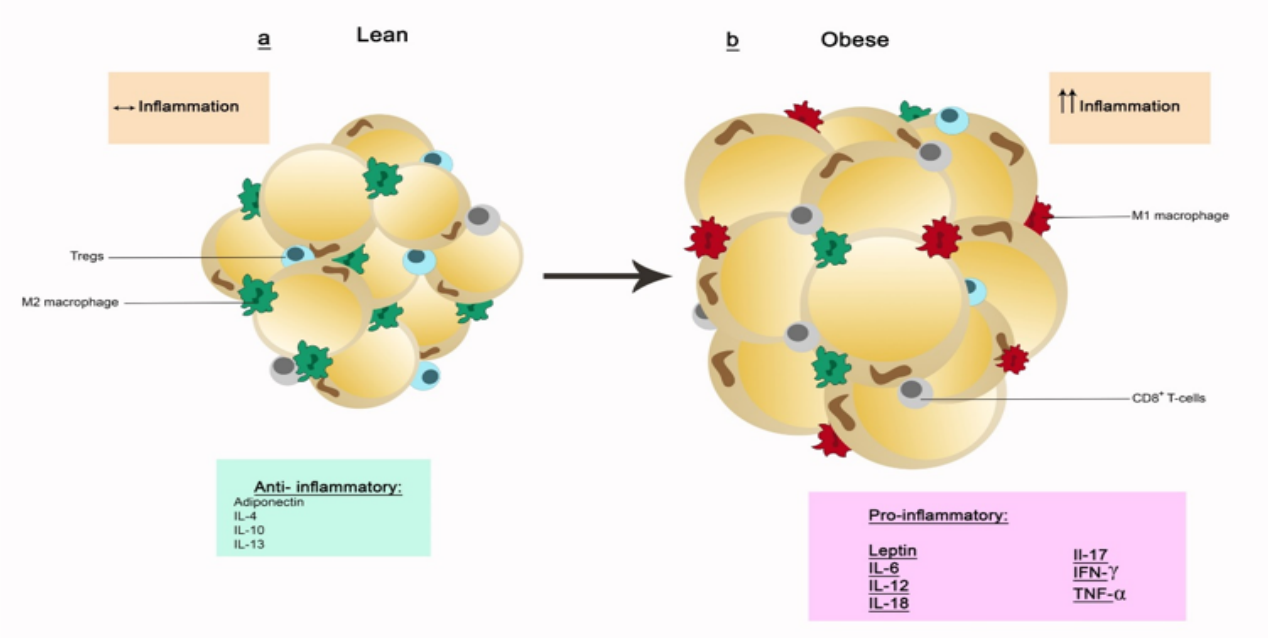

Figure 2. Obesity-related alternation in the immune system.
a. adipocytes in the lean state have normal metabolism and contain cytokines such as IL-4, IL-10, and IL-13, adiponectin as an adipokine, and M2 macrophages **b.** obesity enlarges adipocyte size and switches macrophages to M1 phenotype. Moreover, pro-inflammatory cytokines like IL-6, IL-12, IL-18, IL-17, IFN-γ, TNF-α, and adipokines (leptin) are increased.

flammatory cytokines (TNF-α and IL-6) have oncogenic effects in obese individuals (61).

NF-κB

Nuclear factor-κB (NF-κB), a transcription factor that is crucial for inflammatory reactions, is one of the most significant molecules that link chronic inflammation with cancer, and its activity is closely controlled by several mechanisms (62). NF-κB increases the expression of genes that are related to inflammation and plays a key role in carcinogenesis (63, 64). Activation of NF-κB signaling can affect the immune and inflammatory responses, cell transformation, and expression of genes involved in proliferation, angiogenesis, apoptosis, etc. In the case of cancer, it has been found to impact the same genes involved in tumor growth (65). NF-kB activation induces different target genes such as proliferative and anti-apoptotic genes, and NF-kB signaling crosstalk affects many signaling pathways, including STAT3, AP1, interferon regulatory factors, NRF2, Notch, WNT-β-catenin and p53 (62).

Insulin resistance

Carlsen et al. reported that NF-κB activity in mice fed HFD has increased. Indeed, induced-NF-κB signaling by HFD is more associated with glucose intolerance (66). Inflammation in white adipose tissue is an important factor for insulin resistance. The NK cells and NKT cells in obese patients may act as facilitators for the maintenance of insulin resistance and inflammation of WAT (67, 68). Adipose tissue changes in obesity make insulin to provoke hepatitis production of insulin growth factor-1 (IGF-1). In addition, abnormal serum levels of adipokines, specifically decreased adiponectin levels and up-regulation of leptin leads to the development of hyperinsulinemia and insulin resistance (69). High levels of IGF-1 act as growth factors, which promote cancer cell proliferation and decrease apoptosis. Several controlling pathways modulate the IGF-1 effects, including the (PI3K)–AKT system and the Ras/Raf/ MAPK systems. Overproduction of TNF-α in obesity as a result of inflammatory response is associated with insulin resistance, which also increases the risk of cancer (35). Furthermore, it has been investigated that expression of IL-6, and its circulation is significantly correlated with obesity and insulin resistance (70, 71). IL-6 is able to activate STATE signaling that can stimulate cancer cell proliferation and suppress host antitumor immunity (72). Obesity, along with insulin resistance, activates the NF-κB pathway, which leads to an increase in the target gene expression, which is involved in cancer cell proliferation and anti-apoptosis (73, 74).

Aging

Human aging is an irrefutable issue that is marked by muscle and physiological frailty. Loss of muscle and physical strength is common due to metabolic and biochemical changes. In addition, increased adipose tissue is another common sign of aging and is considered to be an important threat to health (75, 76). In addition, during aging adaptive immune system function is reduced. In contrast to T and B lymphocytes, number of NK cells are increased in aging. Lutz et al have shown the rate of increase in NK cell count is decelerated in obesity (77). The association between the rise in the fat/muscle ratio and immunity in aging is owing to the fact that the expression of anti-inflammatory factors, adiponectin and myokine declines, meanwhile the expression of leptin, TNF-α, IL-1 and IL-6 increases (75, 78-80). In fact, obesity, along with a pro-inflammatory state, may inhibit NK cell functions as well.

Conclusion

The current obesity epidemic is one of the important risk factors for cancer. According to the growing rate of obesity in the young population (23), a better understanding of mechanisms that are associated with cancer and obesity in order to develop effectual prevention and treatment in both disorders is required. Adiposity induces a series of responses, which eventually lead to inflammation and malignancy (17, 81). The tumor microenvironment is a key attribute of the initiation and progression of cancer (82). It has a complex impact on angiogenesis, stroma, fibroblasts, adipocytes, inflammation, and immune systems. Under normal circumstances, stromal components are able to suppress carcinogenesis, which correlates with the survival of the organism. Tumor cells spontaneously can modify stroma, to

synthesize growth factors, cytokines, chemokines and proteases that accelerate disease. Inflamed adipose tissue can strongly influence the tumor microenvironments (83). It probably indicates a correlation between obesity and different types of tumors. Excessive body weight is a kind of stimulus that induces adipocytes to secrete leptin. Our review indicates that a chronic increase in leptin level initiates the cascade of pro-inflammatory signaling, and soon after that, multiple changes occur. Impaired secretion of adipokines (increased leptin and reduction in adiponectin) subsequently affects the immune system function, which reduces the number of Th2 and Tregs and, in contrast, increases the proliferation of Th1 (20). Besides that, several studies have shown diminished immune functions after long-term leptin exposure (16). It seems that short-term and long-term exposure to leptin have opposite stimulatory effects on NK cells. Interestingly, short-term treatment with leptin increases the stimulatory effect, but long-term exposure or leptin resistance impairs immune functions such as reduction of cytotoxicity activity, cytokine secretion, and cell proliferation (84). Accordingly, it has demonstrated a lower activity of NK cells in obese humans compared to lean subjects (85). Studies suggest that leptin-activated NK cells produce IFNγ, which switches adipose tissue macrophages to pro-inflammatory classically activated macrophages. Therefore, it possibly increases cancer susceptibility in obese individuals via altering NK cell's antitumor response. In addition, in obesity, changes in levels of cytokines and, consequently, promotion of insulin resistance cause adipocytes to produce TNF-α, which encourages monocytes to migrate from blood to adipose tissue and start polarizing adipose tissue macrophages to pro-inflammatory activated macrophages (86). Moreover, senescence along with obesity was accessed as a facilitator factor of cancer progression. Thus, adipose-related inflammation regulates tumor growth, progression, and metastasis. It also creates an immunosuppressive environment that debilitates the host to fight against the tumor. However, more extensive research is still needed to bring a transparent picture of precise mechanisms for adipose tissue inflammatory response and how they lead to metabolic alterations and, ultimately, cancer.

Conflict of interests

There is no conflict of interests.

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